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Psychobiology of Threat Appraisal in the Context of Psychotic Experiences: A Selective Review

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Abstract

A key factor in the transition to psychosis is the appraisal of anomalous experiences as threatening. Cognitive models of psychosis have identified attentional and interpretative biases underlying threat-based appraisals. While much research has been conducted into these biases within the clinical and cognitive literature, little examination has occurred at the neural level. However, neurobiological research in social cognition employing threatening stimuli mirror cognitive accounts of maladaptive appraisal in psychosis. This review attempted to integrate neuroimaging data regarding social cognition in psychosis with the concepts of attentional and interpretative threat biases. Systematic review methodology was used to identify relevant articles from Medline, PsycINFO and EMBASE, and PubMed databases. The selective review showed that attentional and interpretative threat biases relate to abnormal activation of a range of subcortical and prefrontal structures, including the amygdala, insula, hippocampus, anterior cingulate, and prefrontal cortex, as well as disrupted connectivity between these regions, when processing threatening and neutral or ambiguous stimuli. Notably, neural findings regarding the misattribution of threat to neutral or ambiguous stimuli presented a more consistent picture. Overall, however, the findings for any specific emotion were mixed, both in terms of the specific brain areas involved and the direction of effects (increased/decreased activity), possibly owing to confounds including small sample sizes, varying experimental paradigms, medication, and heterogeneous, in some cases poorly characterised, patient groups. Further neuroimaging research examining these biases by employing experimentally-induced anomalous perceptual experiences and well-characterised large samples is needed for greater aetiological specificity.

Keywords: psychosis, threat processing, neuroimaging, appraisal, cognitive bias

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1. Introduction

Cognitive models state that a key factor in the transition to psychotic symptoms is the negative interpretation or ‘appraisal’ of anomalous perceptual experiences[1-5]. Maladaptive appraisals endorsed by patients typically represent perceptions of externalised, personalised threat[6-8]. Attentional and interpretative cognitive biases are considered to underlie these threat-based appraisals[2]. An attentional bias would relate to threatening perceptual cues taking on excessive salience, while an interpretative bias would refer to the misinterpretation of neutral or positive stimuli as threatening. These cognitive biases are considered to be transdiagnostic, helping to explain maladaptive cognition in anxiety and depression, as well as psychosis[9]. Additionally, while these biases may help give rise to paranoid delusions, they are not specific to any sub-type of psychosis, instead thought to primarily contribute to the distress associated with positive symptoms[3,10].

These biases are well-established within the clinical literature, with a growing body of research in which tasks designed to mimic anomalous perceptions have been used to investigate appraisals experimentally[11-13]. Although attentional and interpretative biases have not been incorporated into the neurobiological literature[1], there are substantial experimental and neuroimaging data on threat processing in anxiety and psychosis[14]. Findings in social cognition and the neuroscience of threat echo cognitive accounts of appraisal in clinical research, even employing analogous terminology[15].

Within the social cognitive literature, appraisal is taken to mean the classification of stimuli with regards to their emotional-motivational significance, an important determinant of emotional response[16,17]. In essence, appraisal establishes the personal relevance of environmental stimuli according to the individual’s concern for well-being, based on needs, goals, and beliefs[17,18].

‘Threat appraisal’ therefore denotes classifying a stimulus based on its capacity for harming the organism[19]. A possible negative outcome of this adaptive mechanism, having evolved to assist effective threat detection[14], is that threat cues can take on excessive salience, creating a hyper-vigilance or attentional bias towards threat[20,21]. This attentional bias has been observed

behaviourally in delusion-prone individuals[22] and psychosis patients, in studies where participants evaluate positive and negative facial emotions[14,23].

Furthermore, evidence suggests that psychosis patients experience strong aversive emotion when processing neutral stimuli[24,25]. Instead of an impairment for neutral valence recognition, this aversive response may reveal an interpretative bias where neutral/ambiguous stimuli are processed as negative. Taken together, these findings suggest that at the core of threat appraisals are two cognitive biases, namely an attentional bias and an interpretative bias towards threat.

Despite this apparent overlap between clinical and social cognitive conceptions of threat appraisal and its underlying biases, little neuroimaging research has directly examined attentional and interpretative biases, beyond cohorts of anxiety patients[26]. Nonetheless, an acceptable proxy may be to survey existing neuroimaging studies of emotion perception in psychosis[15,27,28], and interpret their findings within the context of attentional and interpretative biases. Facilitating this interpretation is a model of aberrant emotion perception in schizophrenia[29]. Derived from structural and functional neuroimaging studies, it outlines two negatively correlated networks, the ventral and dorsal systems. The ventral system links the ventrolateral prefrontal cortex (PFC), orbitofrontal cortex, ventral anterior cingulate (AC), amygdala, insula, ventral striatum, and the brainstem nuclei, is considered to process identification of the emotional significance of a stimulus, and is largely automatic. Concomitantly, the dorsal system, comprised of the dorsolateral and dorsomedial PFC, dorsal AC, and the hippocampus, is implicated in the effortful regulation of resultant affective states. Utilising this model, this review evaluated the current evidence for the neural underpinnings of attentional and interpretative biases in psychosis.

2. Methods

Systematic review methodology was used to identify relevant articles[30]. A search strategy combining subject headings and text words relating to psychosis, schizophrenia, paranoid, persecutory, cognitive models, appraisal, attention, referential, threat, need for care, bias, and neuro\$ (truncated), was devised and adapted for the electronic databases Medline, PsycINFO and EMBASE

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(1806 to May 2015), as well as on PubMed. See flow chart (Fig. 1) for a detailed description of the selection process.

Neuroimaging of attentional and interpretative biases towards threat is yet to be conducted in psychosis populations. Neuroimaging studies of emotion perception in psychosis provide the nearest analogue, but are varied in their design, making it difficult to outline a typical study design for inclusion in this review. Of those included, the majority of studies asked participants to evaluate different facial emotions in a variety of paradigms, either explicitly or implicitly, comparing brain activation of patients and controls in between-participants or mixed designs. Typically, explicit evaluation of facial emotions referred to tasks in which participants labelled or evaluated the emotions as positive or negative, while implicit paradigms equated to passive viewing of facial emotions, or to their exposure while performing a task, such as labelling gender. Only studies using images of direct and indirect social threat, namely angry and fearful faces, were considered. Although the International Affective Picture System[IAPS; 31] images are often employed to study emotion, such studies were excluded due to their lack of specificity to social threat.

Studies were divided into two categories: those relevant to an attentional bias towards threat, and those potentially revealing an interpretative bias. Assigning studies to one category over another was occasionally a compromise, since there is no perfect theoretical overlap between cognitive models of psychosis, and social cognitive research into threat processing. Nonetheless, studies were considered relevant to elucidating the neural correlates of an attentional bias if activity was recorded in the dorsal and ventral systems while patients were exposed to angry or fearful faces, and of an interpretative bias toward threat if exposed to neutral or happy faces.

Specifically, a desirable outcome was a group×stimulus interaction wherein patients showed patterns of activity different from controls when processing neutral or threatening stimuli, although studies finding no differences were also included. Behavioural or self-report data corroborating these findings, such as patients mislabelling neutral faces as angry or fearful, were considered.

3. Results

Thirty-three papers were included, 25 examining attentional and 8 examining interpretative biases toward threat along with relevant neuroimaging findings.

[INSERT TABLE 1 HERE]

3.1. Findings for an attentional bias towards negative stimuli in psychotic patients

In the 25 studies identified as pertaining to an attentional bias toward threat, the regions most strongly implicated in the abnormal processing of threat were the amygdala, various PFC regions, AC, hippocampus, and the insula. Overall, these studies yielded mixed findings of the direction of change in activity in different regions when exposed to threat.

For the amygdala, five studies observed an under-activation in patients compared to controls when viewing angry/fearful faces[32-36] but three others found no group differences[37-39]. A key study was conducted by Blasi et al.[40], examining drug-naïve schizophrenia patients after 4 and 8 weeks on Olanzapine (an atypical antipsychotic). During implicit and explicit processing of fearful/angry faces, patients exhibited greater amygdala activity but reduced ventrolateral PFC activity at the 4 week mark, relative to controls. At 8 weeks, this relationship was reversed. Intriguingly, a recent study of drug-naïve, first-episode psychosis patients found the reverse[41], in that amygdala activity increased in patients when exposed to angry faces, compared to controls, only after treatment with atypical antipsychotics. It is worth noting, however, that in the Bergé et al. study, patients were only tested upon showing clinical improvement, between 2 and 6 months after entering the study. This makes it impossible to separate the effects of medication from clinical state, although amygdala activity did not correlate with symptoms before or after treatment. In addition, 3 of the 6 experimental blocks presented to participants featured happy faces, while the remaining 3 emotions assigned a single block each, limiting the power to obtain reliable data.

A further study found reduced amygdala activity when viewing fearful faces in patients on typical antipsychotics, compared to controls and patients on Risperidone, an atypical

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antipsychotic[42]. There was no significant difference in amygdala activation between patients on Risperidone and controls. Ventromedial PFC activity of patients on typical antipsychotics, however, was higher than controls and patients on Risperidone, when viewing fearful faces.

Findings were also diverse regarding the group difference in PFC and ACC activity[37,38,43]. Interestingly, one study found that PFC activity of patients, unlike controls, did not co-modulate with dorsal AC activation[43], potentially reflecting disrupted connectivity between these regions.

Behaviourally, results were similarly varied. Four studies found no differences between groups[32,33,42], apart from a slower response in patients[43]. Four studies found that patients performed worse than controls on emotion discrimination tasks, albeit for fearful faces only[34,37,44,45]. In one study this finding was more pronounced in paranoid patients[45]. Finally, one study found patients to be less accurate than controls at identifying all emotions[36].

A potential confound may be the way trials/emotions were contrasted during analyses. A recent meta-analysis demonstrated that many findings of reduced amygdala activity are not due to a diminished response to negative emotional stimuli, but to an exaggerated negative response to neutral stimuli (see below), which may confound results when contrasting neutral vs. emotion trials[46]. Many of the studies reviewed here used neutral faces, rather than baseline activity or other stimuli such as an empty oval shape or fixation cross, as the control condition.

A few studies using non-neutral face control conditions showed hypo-amygdala activity[47,48], but hyper-dorsal PFC activity[49,50] in patients. This pattern was interpreted as reflecting compensatory activity, in that dysfunctional 'automatic' limbic activation may place greater demands on 'conscious' prefrontal structures. One study found no difference in amygdala activity between patients and controls, but increased medial PFC and AC activity, albeit for both angry and neutral faces combined[51]. This was interpreted as an increased perception of social threat generally, potentially showing an overlap between attentional and interpretative biases towards threat.

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One study, unique in design, had psychotic patients view angry and fearful faces (with an oval shape as control) before and after a course of Cognitive Behavioural Therapy for psychosis [CBTp; 52], which targets maladaptive appraisals[53]. After CBTp, patients showed attenuated activity in the ventrolateral PFC, anterior insula, thalamus, putamen and occipital areas while viewing aversive stimuli. This in turn corresponded to reduced symptom severity, particularly persecutory and delusional ideation. Significantly, while anxiety dropped after CBTp, this symptom was not as strongly affected by CBTp as persecution and delusions. Consequently, it is unlikely that these results can be explained by a general reduction in anxiety. The authors concluded that CBTp produces a beneficial effect on the neural processing of threat.

Holt et al.[54] examined threat processing in psychosis by measuring habituation of haemodynamic response over time. Compared to controls, patients did not exhibit response habituation in the medial temporal lobe to fearful faces. Controls exhibited greater habituation than patients in right-hippocampal activity. Initial hippocampal activity was comparable in both groups, suggesting that this reduced habituation did not relate to lowered initial activation of the hippocampus.

Behaviourally, the only notable group difference found across studies employing non-facial baseline conditions was a slowed response in patients[42,47,49,54-56], although one study found patients to be less accurate than controls at identifying all emotions[41].

3.2. Misattribution of threat to neutral or positive stimuli

Eight studies were considered to reflect an interpretative bias towards threat, in which neutral or positive stimuli were interpreted as threatening by patients. The most commonly implicated regions were the amygdala, PFC, cingulate, hippocampus, and parahippocampal gyrus.

Recent studies have shown that patients are more likely to respond neurally to neutral faces as threatening, and show hyper-amygdala activity[56,57]. One study with an implicit perception task found hypo-amygdala activation to fearful compared to neutral faces in patients, relative to

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controls[58]. When response to neutral faces was compared to baseline activity however, amygdala hyper-activation was found in patients, suggesting that hypo-amygdala response to fearful faces was a consequence of an inappropriate fear response to neutral faces. Likewise, Holt et al.[57] found greater amygdala (and hippocampus) activity in patients vs. controls when passively viewing neutral faces.

Surguladze et al.[59] also found raised right parahippocampal gyrus activation for neutral faces, a region with direct connections to the amygdala and hippocampus, in patients versus controls. This abnormal activation correlated with severity of reality distortion, which was also correlated with amygdala activity. Reality distortion being a marker of hallucinations and delusions, this finding provides further evidence for a misattribution of threat to ambiguous stimuli. Interestingly, fearful faces elicited reduced right parahippocampal activation in patients, compared to controls, potentially reflecting an attentional shift away from threatening stimuli in patients.

Similarly, Seiferth et al.[60] examined neural response to emotional and neutral faces during an explicit discrimination task in controls and those at risk for psychosis. Behaviourally, there were no group differences in emotion discrimination, and increased occipital and temporal activation was found in high-risk participants, relative to controls. When specifically processing neutral expressions, increased activation in high-risk participants occurred in the amygdala-hippocampal complex, thalamus and the ventral and dorsal PFC, compared with controls. This finding suggests a hypersensitivity to attributing salience to irrelevant stimuli in prodromal individuals.

One study, employing an explicit affect identification task, initially found reduced dorsomedial PFC and dorsal AC activity and increased cuneus and occipital activity in patients viewing fearful faces, compared with controls[61]. A similar picture emerged with angry faces wherein patients exhibited reduced activation in various regions including the dorsal AC, ventrolateral PFC and parahippocampal gyrus, but showed stronger activity in regions such as dorsolateral PFC, cuneus, and medial PFC. These mixed findings may indicate poor recruitment of regions thought to regulate emotional states, coupled with increased visual cortex activity, potentially implying increased attention given to threatening stimuli in patients. This same study also found that neutral faces elicited

activity and behavioural responses relating to threat, indicative of a misattribution of threat to ambiguous social stimuli in patients, compared to controls. Not only were patients more likely to mislabel neutral faces as fearful/angry, but they also showed increased activation in the dorsolateral and ventral PFC, visual cortex, putamen, parietal lobules and precuneus, relative to controls. Many of these regions are relevant to both the identification of the emotional significance of a stimulus and the regulation of resulting emotional states, indicating a tendency to erroneously attribute threat to neutral/ambiguous stimuli in psychotic patients.

Mier et al.[62] found that not only patients showed less accuracy in identifying neutral faces specifically, but when making errors they were more likely to label both neutral and happy faces as negative, showing a negative bias that in turn correlated with amygdala activation when viewing neutral faces. Hypo-amygdala activation was found in patients relative to controls when viewing happy faces, although neutral faces were used as the control condition. It is therefore possible that amygdala response to happy faces in patients would have been greater had non-facial stimuli been used as the control.

Most studies found no behavioural differences between patients and controls[56,60,63]. Of those that did, impairment in patients related solely to fearful/angry faces[58,61], apart from one study discussed above[62].

3.3. Interaction between systems implicated in emotion perception

Few studies have examined the interconnectedness of the frontal and subcortical regions involved in emotion perception in psychosis. As summarised earlier, Taylor et al.[43] reported findings suggestive of disrupted connectivity between the PFC and AC in patients, a common finding among connectivity studies.

Fakra et al.[49] conducted an interaction analysis on whole-brain fMRI data while participants labelled or matched emotional faces. During the more cognitively demanding labelling task, activity in frontal, temporal, and visual regions was negatively correlated with amygdala activity

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while activity in the right ACC, hippocampus, and visual cortex was positively correlated, in controls. In patients, no regions covaried with activity in either the left or right amygdala, regardless of the task.

A similarly disrupted amygdalo-cortical relationship was observed in Satterthwaite et al.'s study[55], wherein patients exhibited reduced negative correlations between the amygdala, right dorsal and ventral PFC regions, right insula, midbrain, and right inferior parietal lobule. Of note, the authors examined recognition memory for threatening facial expressions, which may demand greater recruitment of cortical regions.

Das et al.[34] found opposite patterns of functional coupling between patients and controls during implicit and explicit perception of fearful faces. During explicit processing, controls showed positive coupling of amygdala activity with the dorsal AC, and negative coupling with the ventral AC. Conversely, amygdala activity in patients only coupled with the ventral AC, and in the opposite direction (positive). Amygdala activity also covaried positively with the thalamus, but only in controls. Similarly, during implicit fear processing, activity in patients showed functional coupling opposite to that of controls between the amygdala and rostral regions of the medial PFC and AC. This implies disruption to both the automatic and regulatory systems involved in emotion perception. Interestingly, this did not correlate with antipsychotic dosage. In a similar study, neither antipsychotic dosage, nor symptom severity correlated with the reduced connectivity observed between the bilateral amygdala and several brain regions, when contrasting implicit perception of angry versus fearful faces in patients relative to controls[64].

Conversely, Rasetti et al.[65] found that functional decoupling between limbic and cortical regions did correlate with antipsychotic dosage. Patients implicitly processed angry/fearful faces, with a shape-matching task used as a control condition.

4. Discussion

Taken together, the literature provides evidence for abnormal neural responsivity to threat in psychosis, relating to both an attentional bias towards threatening stimuli and a misattribution of threat to neutral or even positive stimuli. The brain regions implicated are common to models of dysregulated emotion processing proposed to account for threat salience in anxiety[66], as well as threat misattribution in psychosis[29].

The majority of studies reviewed focused on differential activity in subcortical regions involved in the identification of a stimulus' emotional significance, primarily the amygdala, but also the insula, thalamus and visual cortex, and in regions considered to regulate affect, primarily the PFC, AC and hippocampus. Incidentally, this gross distinction in functioning between subcortical and cortical regions was reasserted in most studies, despite evidence that some of these structures exhibit both ventral and dorsal streams which aid in emotional significance identification and affect regulation respectively[29].

Many studies used contrast paradigms in which neural response to negative emotion was subtracted from neutral emotion, rather than baseline activity. This, while appropriate for studying emotion processing in healthy groups, arguably confounded results in psychotic patients due to neutral faces eliciting aberrant emotional salience in schizophrenia[46].

4.1. Evidence for an attentional bias towards threat in psychosis

Focusing on studies employing appropriate contrast paradigms, results were still mixed. The direction of change in neural activity in each region when responding to threat (fear/anger) varied across studies. Some found no group differences or reduced amygdala and prefrontal activity in patients and those at high-risk for psychosis[47,48,61], whereas others found seemingly compensatory increases in activity of regulatory structures such as the dorsomedial PFC and hippocampus[49,50,54].

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Overall, most studies focused on threat processing via the amygdala, finding reduced activation in patients relative to controls when processing threat. Although this was often interpreted as a deficit in emotion identification in schizophrenia, there are several confounding factors that provide alternative interpretations. Amygdala activity may habituate too quickly for some paradigms to be sensitive to temporal change in response[56,57], and patients may be more likely to experience sustained fear (a more long-lasting state of apprehension/anxiety to a diffuse cue, or a set of cues, occurring unpredictably) than phasic fear, measured mostly in response to a short, discrete fear-inducing stimulus that begins rapidly with stimulus onset and dissipates once the stimulus is removed[67].

Another confound is antipsychotic medication, with three studies finding conflicting data regarding the effects of typical and atypical antipsychotics on amygdala and PFC activity when viewing angry/fearful faces, whether in drug-naïve[40], first-episode[41], or patients on maintenance doses[42]. These findings suggest a differential impact of antipsychotic type and dosage, as well as potential interaction effects of medication and clinical state on neural activity, which should not be ignored in future studies.

Another issue warranting further attention is connectivity. The few studies examining functional connectivity consistently found that the anticorrelation typically expected between subcortical and frontal networks during threat processing was disrupted in patients[34,49,55], with one study finding that this functional decoupling correlated with antipsychotic dosage, regardless of medication type[65].

Taking these various confounds into account, there appears to be abnormal functioning and connectivity between the structures involved in the identification and regulation of affect in psychosis when processing threat. It remains unclear whether excessive threat salience relates to an over-recruitment of ‘ventral’ structures such as the amygdala and insula, an under-recruitment of ‘dorsal’ structures such as the hippocampus and dorsomedial PFC, or a dysfunctional interaction between ventral and dorsal systems.

Regarding the integration of cognitive research on maladaptive appraisals with neurobiological findings relating to threat processing in psychosis, the most pertinent study may be the one[52] examining responses to angry/fearful faces before and after CBTp, revealing diminished activity in the ventrolateral PFC, anterior insula, thalamus, putamen and the visual cortex post-CBTp. Since these regions are relevant to the identification of a stimulus' emotional significance, the implication is that CBTp, which targets threat-based appraisals of anomalous experiences, helps reduce aberrant threat salience. Furthermore, patients' medications did not change, excluding medication effects as a potential confound.

4.1.1 Evidence for an interpretative bias towards threat in psychosis

It was found that in addition to exhibiting abnormal neural responses to threatening stimuli, psychosis patients tend to exhibit heightened emotional processing when viewing neutral faces contrasted with baseline activity, implying the misattribution of threatening emotional content to neutral stimuli[54,58-62]. In two studies, this was corroborated behaviourally, with patients more likely to misidentify neutral faces as fearful or other negative emotions[61,62]. Despite few studies available for review, the overall finding in patients was increased activity in regions central to both the 'ventral' and 'dorsal' emotional processing streams, including the amygdala, hippocampus, AC, PFC and parahippocampal gyrus. Remarkably, one study reported heightened amygdala activity in patients, compared with controls, in response to happy faces, despite no group differences for angry faces[63]. Although not meeting inclusion criteria for this review, other studies echo this finding. One experiment played positive and threatening words to patients with chronic auditory hallucinations[68]. Relative to controls, enhanced activity was observed in response to emotional words, whether positive or negative, in a number of regions, including the frontal lobe and the amygdala. A more recent study with an identical paradigm found elevated amygdala and parahippocampal activation in patients with chronic voices, relative to patients without auditory hallucinations, and controls[69]. While these findings may reflect the misattribution of threat to neutral or even pleasant stimuli, it is worth noting that the words were selected for their high frequency in patients' psychoses, so the self-relatedness of each word may have contributed to the augmented responses.

Overall, the limited literature supports the notion of a biased evaluation of neutral or even positive social stimuli as being hostile in psychotic illness, where increased activity is observed in regions relevant to both significance identification and affect regulation, despite neutral content.

4.2 Methodological issues

A significant methodological issue may relate to the effects of medication[40-42,65]. Notably some patients may also be on anxiolytic or antidepressant medication, likely to alter affective processing[70].

Another is that amygdala responsivity to threatening contexts may be time-limited[71]. Amygdala response quickly habituates with repeated presentation of facial expressions, hence blocked designs may lack sensitivity in detecting rapid attenuation of amygdala activity[72,73]. A study examining medial temporal lobe activation during passive viewing of happy, angry, and neutral faces provided evidence to this effect[57]. While viewing fearful and neutral faces, greater right amygdala and hippocampus activation was observed in schizophrenia patients relative to controls, albeit only during the first of two blocks of faces.

Suslow et al.[56] split their trials of implicitly shown angry, happy, and neutral faces into two phases of equal length. During the initial phase, patients exhibited increased right amygdala response to all expressions, as well as a significant increase in left amygdala response to neutral faces, compared with controls. During the second phase, it was controls who displayed a higher response in the right amygdala to all expressions. The authors interpreted this switch in patients as representing a blocking mechanism, potentially to avoid overstimulation during social interaction.

Another potential confound is that most experimental paradigms tap into 'phasic' rather 'sustained' fear[74]. Fear and anxiety are not necessarily synonymous[71]; while fear may be stimulus-bound and temporally specific, anxiety may not necessarily be elicited by specific threatening stimuli, but rather a consistent state of 'sustained fear'. Anxiety symptoms are better detected using experimental paradigms tapping into sustained rather than phasic fear[74].

Outside of these principal methodological confounds, some important limitations were identified. Sample sizes were frequently low. Although small samples are typical for fMRI studies, low statistical power is nonetheless a common problem[75]. There was also variability in analyses, i.e. whole-brain vs. region of interest (ROI). Although ROI analysis focuses on a single region, avoiding multiple comparisons, whole-brain analysis is preferable given that a network of regions is involved in emotion processing[29]. Regardless, the choice of analysis will impact on the statistical power required to find an effect, in addition to sample size.

Gender and age were often unbalanced within- and between-groups across studies, as was illness severity. Interestingly, a recent meta-analysis of fMRI studies employing facial emotion tasks found no effect of gender, but age correlated with higher, and increased symptom severity with lower, parahippocampal gyrus activity[27].

Few studies explicitly stated whether their patient samples were chronically ill and/or symptomatic. Although a recent meta-analysis of the neural correlates of facial emotion processing in schizophrenia found that limiting analysis to chronic patients did not significantly alter results[28], some effects may occur only in specific sub-groups, e.g. differential activation patterns to facial affect in paranoid and non-paranoid patients[35,44,45]; an exaggerated response to physical threat in those with a history of violence[76], or a markedly reduced amygdala response to fearful faces in those with psychopathy[77]. Unfortunately, few studies recruited patients with schizoaffective disorder, limiting the findings to schizophrenia populations. Even correlating neural activation with different symptoms might present divergent findings, given the heterogeneity of the disorder[78].

The use of explicit (affect labelling) and implicit (age/gender discrimination) tasks varied across studies. Again, the effects of psychotic symptoms and antipsychotic medication in this context are unknown. A recent study with healthy controls found that explicit emotion labelling elicited greater bilateral amygdala activation than the implicit task[79], although a meta-analysis looking at patient data did not[28], and another study found the opposite result[80].

Overall, further studies should strive for bigger sample sizes, and stratify patient samples by medication, age, illness stage, symptom severity and social functioning. Task design should attempt to tap into both ‘sustained’ and ‘phasic’ fear, and allow early and late phases of the task to be examined together but also separately. Analyses should prioritise whole-brain and functional connectivity analysis, and examine neural responses to direct (anger) and indirect threat stimuli (fear) separately and relative to an appropriate control (e.g. a scrambled face) rather than a neutral face. Finally, future neuroimaging studies wishing to examine threat appraisal in psychosis should look beyond facial emotion paradigms. Adapting paradigms with greater ecological validity for use with neuroimaging would be helpful, such as virtual reality studies of the paranoia continuum[81]. Looking beyond social threat may also prove fruitful. For instance, a recent study showed that schizophrenia patients may be more accurate when detecting non-social threat (e.g. snakes) than angry faces[82]. Experimentally-induced anomalous experiences studies would also benefit from investigation using neuroimaging techniques[11,13]. The challenge remains to successfully adapt and test these varied paradigms within a neuroimaging environment.

5. Conclusions

Attentional and interpretative biases towards threat play a central role in the development and maintenance of psychosis. It is of interest to investigate these biases not as peripheral, but aetiologically relevant, integrating these concepts with neurobiological findings[1]. This review examined neuroimaging findings relevant to the potential neural correlates of these biases.

Findings map onto a model of emotion processing in schizophrenia involving negatively correlated activity between a regulatory ‘dorsal’ system, and a ‘ventral’ emotional significance identification system[29]. Abnormal activity in these systems relates to biased attention towards and away from threat in affective disorders[66]; the modest literature reviewed suggests this may also be the case in psychosis.

Findings are mixed, however, as the direction of change in neural activation in patients compared to controls when exposed to threatening social stimuli varies across studies, potentially due

to multiple sources, such as the paradigms used and length of medication use. Rather, it seems that a more pronounced phenomenon in psychosis is the misattribution of hostile intent to neutral or positive social stimuli. Nevertheless, both sets of neuroimaging findings correspond to an extent with cognitive and behavioural research into attentional and interpretative biases that drive maladaptive appraisals central to developing a need-for-care.

Despite many of the studies cited having previously been summarised in meta-analyses[27,28], this review examined their findings in the context of threat appraisal in psychosis, and found them lacking in consistency, but also specificity. Clearly, there is a need for more direct investigation of the neural mechanisms underlying attentional and interpretative threat biases, so as to successfully integrate cognitive models of psychosis with their potential neural substrates. To this end, novel paradigms with greater specificity to psychosis should be employed, such as anomalous experience-inducing tasks, which have been effective at eliciting threat appraisal in experimental studies[11,13]. Additionally, recruiting individuals across the psychosis spectrum, both in terms of specific psychotic disorders, as well as intensity and frequency of symptoms, would further help to evaluate the cognitive model of psychosis, which adopts a continuum view of psychosis[5]. Ultimately, clarifying the neural networks pertinent to threat appraisal has the potential to increase the focus and efficacy of therapeutic interventions targeting maladaptive appraisals in psychosis.

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Table 1

Summary of neuroimaging findings relevant to threat processing in the context of psychotic experiences.

Publication	Design & Participants (M/F)	Emotion processing task (fMRI design)	Modality (Analysis approach)	Main observations
Attentional bias for threat				
Bergé et al., 2014 [41]	Mixed design Group 1: 18 (10/8) first psychotic episode, all on atypical antipsychotics Group 2: 19 (9/10) Healthy Controls	Emotion discrimination task with angry, fearful, happy, and disgusted faces presented alongside neutral faces, with a low-demand cognitive task using geometric shapes as control condition (presented in blocks).	fMRI (whole-brain, with ROI approach for the amygdala)	Two scans, one during acute episode, one upon clinical improvement. Behaviourally, patients significantly less accurate than controls, across all conditions. Post-hoc tests revealed patients significantly worse than controls at discriminating anger from neutral and disgust from neutral at pre-treatment, and anger and happiness in the post-treatment scan. Neurally, significant interaction between group and treatment: Reduced activation in hippocampus and amygdala in patients, relative to controls, across conditions at pre-treatment, but not post-treatment. Significant group x task condition x treatment interaction: pre-treatment bilateral amygdala activation in response to anger equivalent between groups, but post-treatment activation higher in patients, relative to controls.
Mothersill et al., 2014 [51]	Between-groups Group 1: 25 (20/5) SP/SAD, all on antipsychotics* Group 2: 21 (16/5) Healthy Controls	Passive viewing of 2-5sec black & white videos with neutral faces becoming angry or neutral/ambiguous. Black & White concentric circles expanding acted as baseline (block-design)	fMRI (whole-brain)	Significant effects of group, and of condition separately, but no significant group x condition interaction: Patients, compared to controls, showed increased activity in the medial PFC and ACC, and decreased activity in left cerebellum, across conditions. Comparing angry faces with baseline, patients showed weaker deactivation of the medial PFC and ACC. Non-significant altered activity in medial PFC was observed when comparing neutral faces with baseline.
Suslow et al., 2013	Between-groups Group 1: 30 (17/13) SP, all	Explicit evaluation of implicitly shown (masked) angry,	fMRI (whole-brain, ROI approach for	No group differences in positive/negative evaluative ratings of faces. Neurally, across groups, bilateral amygdala activation in response to all faces stronger in first phase than

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[56]	on atypical antipsychotics Group 2: 35 (23/12) Healthy Controls	happy, neutral facial expressions, with empty oval face as control condition. Task split into two phases of equal length (presented randomly in an event-related design)	the amygdala)	second. During initial phase, patients exhibited increased right amygdala response to all faces and increased left amygdala response to neutral faces. In second phase, controls displayed higher right amygdala response to all faces and higher left amygdala response to angry faces.
Villalta-Gil et al. 2013 [39]	Between-groups 22 (13/9) first psychotic episode, all on antipsychotics* 31 (15/16) Healthy Controls	Explicit and implicit processing (emotion, identity or gender matching) of fearful and happy facial expressions at half and full intensity, with neutral faces as control condition (block design)	fMRI (whole-brain)	Behaviourally, patients performed significantly slower and less accurate than controls, in all conditions. Neurally, significant effects of task demand, emotion, and intensity on patterns of activation, but only in controls. No significant interaction or group effects.
Li et al., 2012 [37]	Between-groups Group 1: 12 (6/6) SP Group 2: 12 (4/9) non-psychotic siblings Group 3: 12 (6/6) Healthy Controls	Explicit positive/negative evaluations of happy and fearful faces, with neutral faces as control (event-related)	fMRI (whole-brain, followed by ROI approach for the amygdala)	Behaviourally, patients were significantly less accurate than controls and siblings when judging fearful faces. Neurally, when processing fearful faces, patients showed reduced activation in dorsolateral and dorsomedial PFC and greater activation in left rostral PFC; siblings, relative to patients, showed greater activation in right postcentral gyrus but lower activation in bilateral middle frontal gyri, right orbital frontal gyrus, and left middle temporal gyrus. For fearful faces, controls showed significantly lower activation than siblings in right precentral and superior frontal gyri. No group differences for amygdala activation.
Mukherjee et al., 2012 [64]	Between-groups Group 1: 19 (12/7) SP, all on antipsychotics*	Implicit emotion perception of fearful and neutral faces, with a fixation cross	fMRI (whole-brain, followed by ROI approach for the	Behavioural data not reported. Contrasting response to fearful faces with neutral faces, a PPI analysis revealed significantly reduced effective connectivity between the amygdala and various regions of the brain, particularly the

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	Group 2: 24 (16/8) Healthy Controls	as a control condition (block design)	amygdala)	inferior parietal lobule, in patients relative to controls. No other neural differences. No significant correlation between connectivity and antipsychotic dosage, or symptom severity.
Kumari et al., 2011 [52]	Within-groups Group 1: 22 (18/4) SP+CBT Group 2: 16 (14/2) SP+TAU all stable on antipsychotics*	Implicit emotion perception of neutral, fearful, angry, happy facial expressions, with empty oval frame as control (block-design)	fMRI (whole-brain)	Significant effect of CBTp: CBT for psychosis group showed decreased activation of ventrolateral PFC, anterior insula, thalamus, putamen and occipital areas for fearful and angry faces at follow-up, but not TAU group. Activity reduction during angry (but not fearful) expressions correlated with reduced positive symptom severity.
Pinkham et al. 2011 [36]	Between-groups Group 1: 31 SP, 4 SAD (17/18) Group 2: 37 (18/19) Healthy Controls	Emotion identification of angry and fearful expressions, with either direct or averted gaze, with neutral faces as control (event-related)	fMRI (whole-brain, with ROI approach for the bilateral amygdala)	Behaviourally, controls significantly more accurate than patients. Additionally, across groups, direct-gaze anger and averted-gaze fear were better recognised than averted anger and direct fear. Neurally, significant emotion x gaze x group interaction: Patients demonstrated significantly reduced amygdala response to direct-gaze anger expressions, relative to controls, but no differences found across groups in other conditions. In patients, amygdala response to direct-gaze anger correlated positively with level of social functioning.
Surguladze et al., 2011 [42]	Between-groups Group 1: 16 (9/7) SP on conventional antipsychotics Group 2: 16 (6/10) SP on Risperidone injection Group 3: (8/8) 16 Healthy Controls	Implicit emotion perception of happy or fearful faces at half and full intensity, with neutral expressions as the control condition (event-related)	fMRI (whole-brain, followed by ROI approach for amygdala)	No significant behavioural differences across groups and conditions. Neurally, significant effects of group: The control and Risperidone groups displayed similarly heightened activation in the left amygdala when viewing full intensity fearful faces, compared to those on conventional antipsychotics. The conventional group displayed significantly heightened activity in the ventro-medial PFC in response to both full intensity happy and fearful faces, compared with control and Risperidone groups.
Taylor et	Between-groups	Positive/negative	fMRI (whole-brain)	Similar accuracy of valence judgments, although patients

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al., 2011 [43]	Group 1: 16 SP + 5 SAD (14/7) on antipsychotics* Group 2: 21 Controls (15/6)	evaluations of happy, angry, sad, fearful expressions. Neutral faces as control (block design)		slower to respond (esp. negative expressions). Neurally, valence appraisal activated medial PFC across faces /groups. Patients had greater activation of dorsal ACC for negative faces. PPI analysis of dorsal ACC: Significant co-modulation of medial PFC in controls, significantly less in patients, but trend for co-modulation of occipital cortex in patients. Occipital cortex activity correlated with poor social adjustment and impaired social cognition. Poor social cognition correlated with co-modulation of the occipital gyrus by the dorsal ACC.
Satterthwaite et al., 2010 [55]	Between-groups Group 1: 12 SP + 4 SAD Patients (10/6), Group 2: 14 on antipsychotics* 21 (10/11) Healthy Controls	Recognition memory task for threatening (angry/fearful) and non-threatening (happy/sad) faces, baseline activity as control (block design)	fMRI (whole-brain, ROI approach for amygdala, orbitofrontal cortex, lateral and medial parietal cortices, and connectivity analysis for limbic regions)	Similar recognition accuracy, but patients significantly slower to respond, correlating with symptom burden. Neurally, no significant group x face type interaction, however severity of patients' symptoms correlated significantly with augmented amygdala and orbitofrontal cortex response to threatening faces only. Connectivity analysis in patients: Compared to controls, patients showed significantly reduced anticorrelation between left amygdala, right middle frontal gyrus, right inferior parietal lobule, and between the amygdala, right orbitofrontal cortex, right insula, and midbrain.
Blasi et al., 2009 [40]	Mixed design Group 1: 12 (10/2) drug-free Group 2: SP 12 (10/2) Healthy Controls	Implicit and Explicit processing of angry and fearful faces after 4 and 8 weeks on olanzapine. Sensorimotor shape- matching task used as control (block design)	fMRI (whole-brain)	Patients significantly less accurate than controls and slower to respond. In patents, left amygdala activity significantly greater than in controls at first scan during both tasks, but significantly lower at second scan. During implicit processing, right ventrolateral PFC activity lower in patients at first scan and greater at second scan.
Rasetti et al., 2009 [65]	Between-groups Group 1: 34 (25/9) SP on antipsychotics*	Implicit emotion perception of angry and fearful faces, shape-matching	fMRI (whole-brain, ROI approach for amygdala, followed by functional	No differences for accuracy. Neurally, significant group x condition interaction: patients demonstrated decreased amygdala activity for threatening faces. Additionally, patients showed significant decrease in amygdala-subgenual

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	Group 2: 29 (16/13) unaffected siblings Group 3: 20 (15/5) Healthy Controls	sensorimotor task used as control (block design)	connectivity analysis for amygdala and subgenual cingulate)	cingulate functional coupling relative to siblings/controls, and this correlated with dosage of antipsychotic medication.
Fakra et al., 2008 [49]	Between-groups Group 1: 14 (9/5) SP Group 2: 14 (9/5) Healthy Controls	Explicit emotion labelling and implicit perception tasks using fearful and angry faces. Oval shapes as control (Block design)	fMRI (whole-brain analysis, and connectivity analysis for amygdala and prefrontal regions)	Similar accuracy, but patients significantly slower to respond in labelling condition. Neurally, significant effect of condition (explicit versus implicit) but not emotion: In the matching task, activation was significantly lower in patients than controls in bilateral amygdala and putamen, inferior frontal gyrus, hypothalamus, and right superior temporal cortex. Activation significantly higher in patients in left inferior parietal cortex, left medial and superior frontal gyri, left middle temporal cortex and right precuneus. No group differences in activation during labelling task. PPI analysis: right superior and medial frontal cortex, middle temporal cortex and bilateral visual cortex showed negative covariation with left amygdala, whereas right anterior cingulate cortex, hippocampus and visual cortex covaried positively with right amygdala, during labelling condition, in controls only. No regions in patients whose activity covaried with right or left amygdala across conditions.
Michalopo ulou et al., 2008 [33]	Between-groups Group 1: 11 (9/2) SP on antipsychotics* Group 2: 9 (5/4) Healthy Controls	Implicit emotion perception task with fearful faces. Neutral faces as control (event-related design)	fMRI (whole-brain)	No differences in performance. Neurally, significantly higher activation in right amygdala in controls than patients for fearful faces. Amygdala activation did not correlate significantly with positive symptom severity in patients. Patients also had significantly reduced activation in fusiform gyrus, left superior temporal gyrus, bilateral inferior frontal gyri, and right parahippocampal gyrus for fearful faces. Only significant correlation between symptoms and activation was for negative symptoms and left superior temporal gyrus in patients while viewing fearful faces.

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Rădulescu & Mujica-Parodi, 2008 [38]	Between-groups Group 1: 11 (8/3) SP on antipsychotics* Group 2: 11 (8/3) Healthy Controls	Passive viewing of angry, fearful faces. Neutral faces as control (block design)	fMRI (ROI approach for amygdala, hippocampus, and PFC)	No group differences in activation for angry faces, but differences in signal dynamics between excitatory (amygdala) and inhibitory (PFC) components of emotional arousal in both groups. When examining entire time-series, patients had significantly lower activation in PFC at beginning and higher activation in same region towards end of the block, compared to controls. No significant differences in activation or signal dynamics between groups for fearful faces.
Das et al., 2007 [34]	Between-groups Group 1: 14 (14/0) first-episode SP, 5 un-medicated, 9 on atypical antipsychotics Group 2: 14 (14/0) Healthy Controls	Explicit and implicit emotion perception of fearful faces. Neutral faces as control (block design)	fMRI (ROI approach for the amygdala, medial PFC, visual cortex, brainstem. Functional connectivity analysis for these regions)	Patients significantly worse at recognising fearful faces and displayed significantly reduced amygdala activity for fearful faces in both conditions, compared to controls. Connectivity analysis: During conscious perception of fear, contrary to controls, patients displayed positive coupling of the amygdala with ventral ACC, and negative covariation with brainstem. Amygdalar activity covaried positively with the thalamus, but only in controls. During implicit fear perception, patients displayed negative covariation between amygdala and the rostral region of the PFC and ACC, as well as the midbrain, conversely to controls.
Gur et al., 2007 [32]	Between-groups Group 1: 16 (12/4) SP, 15 on antipsychotics* Group 2: 17 (12/5) Healthy Controls	Emotion identification task including happy, sad, angry, fearful facial expressions. Neutral faces for control (event-related design)	fMRI (whole-brain)	Behaviourally, no group differences. Neurally, significant group effect: Patients showed reduced limbic activation (including amygdala) for all faces, compared to controls. In event-related analysis, greater activation in limbic regions in patients correlated with incorrect affect identification, contrary to controls, but only for anger and fear: in fusiform gyrus and amygdala for anger; and amygdala, hippocampus, thalamus, fusiform gyrus, frontal and visual cortices for fear. Positive correlation between severity of affective flattening and greater amygdala response to fearful faces.
Russell et al., 2007 [83]	Between-groups Group 1: 7 (7/0) paranoid chronic SP	Implicit emotion perception (gender discrimination) of fearful faces	fMRI (whole-brain, ROI approach for amygdala-hippocampal)	No group differences for accuracy. Neurally, significant effects of group: Increased hippocampal activation in non-paranoid patients relative to paranoid and controls, regardless of intensity. Paranoid sub-group had decreased

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	Group 2: 8 non-paranoid (8/0) chronic SP, all atypical antipsychotics Group 3: 10 (10/0) Healthy Controls	dynamically increasing and decreasing in intensity. No baseline condition (block design)	complex)	amygdala activity compared to other groups. Paranoid patients also displayed positive hippocampal activation relative to the mean, indicating they did respond to the emerging fear stimuli, and implying that failure to activate the amygdala was not the result of a more general deficit in all neural responses to fear images.
Williams et al., 2007 [44]	Between-groups Group 1: 13 (8/5) paranoid SP Group 2: 14 (9/5) non-paranoid SP, all on atypical antipsychotics Group 3: 22 (17/10) Healthy Controls	Implicit emotion perception task using negative (fearful, angry, disgusted) faces. Neutral faces as control (block design)	fMRI (whole-brain)	Patients significantly worse at identifying fearful faces. Neurally, significant group effects: Both patient groups displayed under-recruitment in amygdala, insula, ventral ACC, hippocampus, and dorsomedial and lateral PFC for anger and fear, relative to controls. Paranoid patients, compared to other groups, showed reduced activation in amygdala and lateral PFC for fear, and the ACC, hippocampus, lateral PFC for anger. Paranoid patients, relative to non-paranoid, but not controls, showed reduction in the medial PFC for anger and fear, and amygdala for fear.
Holt et al., 2005 [54]	Between-groups Group 1: 18 (18/0) chronic SP on antipsychotics* Group 2: 16 (16/0) Healthy Controls	Passive viewing of fearful and happy faces. Baseline activity as control (block design)	fMRI (ROI approach for amygdala, hippocampus, and parahippocampal gyrus)	No group differences for valence ratings, but patients significantly worse than controls at recognising whether face was old or new. Contrary to controls, patients did not show medial temporal lobe habituation for either face. Right hippocampal habituation to fearful faces only was significantly greater in controls than patients.
Johnston et al., 2005 [48]	Between-groups Group 1: 10 (8/2) SP on antipsychotics Group 2: 10 (8/2) Healthy	Attentional tasks (one tracking gender, one emotion) with neutral, angry, fearful, happy, disgusted, surprised	fMRI (whole-brain, ROI for amygdala, middle temporal gyrus, fusiform gyrus, middle occipital gyrus,	Significant effect of group: across gender and emotion discrimination tasks, patients showed reduced activation in fusiform gyrus, inferior frontal, middle temporal and middle occipital gyrus, and amygdala, relative to controls.

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	Controls	faces. Geometric shapes as control (mixed block and event-related design)	inferior frontal gyrus, insula, cerebellum, and cingulate gyrus)	
Williams et al., 2004 [45]	Between-groups Group 1: 13 paranoid SP + 14 non-paranoid SP (17/10) all on atypical antipsychotics Group 2: 22 (14/8) Healthy Controls	Implicit emotion perception of fearful faces. Neutral faces as control (block design)	fMRI (whole-brain)	Patients significantly less accurate than controls in post-scan emotion classification task. Paranoid significantly lower accuracy than non-paranoid for fearful faces only. Neurally, significant group effects: both patient groups showed reduced activity in right amygdala, both medial and lateral PFCs, and bilateral fusiform gyri for fear, compared to controls. Paranoid, compared with other groups, showed reduced activity in amygdala and mPFC. Non-paranoid participants showed reduction, relative to controls, in hippocampal gyrus activity, but not in the amygdala.
Hempel et al., 2003 [50]	Between-groups Group 1: 9 (4/5) partially-remitted first episode SP on atypical antipsychotics Group 2: 10 (6/4) Healthy controls	Emotion matching and labelling tasks with angry, happy, sad, disgusted, surprised, neutral faces. Inverted neutral faces as control (block design)	fMRI (whole-brain)	Accuracy significantly lower in patients for both tasks, relative to controls. Neurally, significant group x condition interaction: patients showed decreased activation, compared to controls, of ACC during affect discrimination and amygdala-hippocampal complex bilaterally in affect labelling. Additionally, statistical trend towards increased activation of dorsomedial PFC in patients compared to controls during discrimination, and higher activation in dorsomedial PFC and posterior cingulate in patients relative to controls during labelling.
Gur et al., 2002 [47]	Between-groups Group 1: 14 (10/4) stable SP, 13 on antipsychotics* Group 2: 14 (10/4) Healthy Controls	Emotional valence and age discrimination of happy, sad, anger, fearful, disgusted faces, neutral faces. Fixation cross for control (block design)	fMRI (ROI for amygdala, hippocampus, fusiform gyrus, occipital lobe)	No significant group differences behaviourally. Neurally, significant group x condition interaction: Patients showed reduced activation, relative to controls, of left amygdala and bilateral hippocampus when discriminating positive from negative facial affect valence.

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Phillips et al., 1999 [35]	Between-groups Group 1: 5 paranoid SP Group 2: 5 non-paranoid SP Group 3: 5 Healthy controls	Passive viewing of fearful, angry, disgusted, happy, neutral faces. Mildly happy faces as baseline condition (block design)	fMRI (whole-brain)	In post-scan emotion identification task, both patient groups significantly less accurate in identifying emotions than controls. Neurally, significant group x condition: both patient groups showed less activation than controls in superior temporal gyrus, amygdala, putamen for fear, as well as inferior frontal gyrus, putamen, cerebellum for anger. Paranoid had greater activity than non-paranoid in cerebellum, insula, visual areas in response to fear. Paranoid showed decreased activation in cerebellum, thalamus, inferior temporal gyrus for anger.
Interpretative bias for threat				
Mier et al., 2014 [62]	Between-groups Group 1: 11 (7/4) SP, all on antipsychotics* Group 2: 16 (11/5) Healthy Controls	Explicit emotion identification of happy, disgusted, angry, and fearful faces, with neutral faces as the control condition (event-related)	fMRI (whole-brain, followed by ROI approach for amygdala)	Behaviourally, patients made significantly more errors when identifying neutral faces, relative to controls. Additionally, when committing errors, patients were significantly more likely to misidentify happy and neutral faces as negative expressions (negative bias). Neurally, significant effect of group across conditions: Whole-brain contrasts revealed reduced activation in temporal and parietal areas in patients compared to controls, while patients showed increased activity in occipital regions relative to controls. ROI analysis for amygdala revealed significantly reduced activation in patients versus controls. Significant group x condition interaction: In patients, relative to controls, reduced amygdala activity in response to happy faces, and, additionally, non-significantly increased amygdala activity when viewing neutral faces. A significant positive correlation between amygdala activation and a negative bias, when viewing neutral faces, but no correlation between medication dosage and activation in patients.
Habel et al., 2010 [79]	Between-groups Group 1: 17 SP Group 2: 17 Healthy Controls	Explicit facial affect labelling of happy, sad, angry, fearful expressions.	fMRI (whole-brain)	Patients significantly more likely than controls to mislabel neutral faces as fearful or angry. Neurally, significant group x condition interaction: for fearful faces, patients showed lower activation in right dorsomedial PFC, right dorsal ACC and bilateral cuneus and higher activation in right precentral

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		Baseline activity as control condition (event-related)		gyri, right putamen, left middle occipital gyrus and left cuneus, compared to controls. For angry faces, patients showed less activation in right superior temporal gyrus, right middle temporal gyrus, right dorsal ACC, right ventrolateral PFC, bilateral cuneus and the left parahippocampal gyrus, relative to controls, but stronger activation in right precentral gyrus extending to the right dorsolateral PFC, right superior parietal lobule, left cuneus and left medial PFC. For neutral faces, patients showed stronger recruitment of right precentral and postcentral areas and right dorsolateral PFC, bilateral putamen, left inferior and right superior parietal lobules, right precuneus, left cuneus, left middle orbital gyrus extending to subgenual cingulate cortex, relative to controls.
Seiferth et al., 2008 [60]	Between-groups Group 2: 12 (10/2) at risk for psychosis, 4 on antipsychotics* Group 2: 12 (10/2) Healthy Controls	Emotion discrimination task with happy, angry, fearful, sad, neutral facial expressions. Baseline activity as control (event-related design)	fMRI (whole-brain)	No group differences in behavioural performance. Neurally, across conditions, emotion discrimination associated with significantly increased activation in high-risk group in right lingual and fusiform gyrus, left middle occipital gyrus. Significant group x condition interaction: high-risk group displayed increased activation for neutral faces in amygdala-hippocampal complex, inferior and superior frontal gyri, cuneus, thalamus and hippocampus, compared to controls.
Hall et al., 2008 [58]	Between-groups Group 1: 19 SP on antipsychotics* Group 2: 24 Healthy Controls	Implicit emotion perception of neutral and fearful facial expressions. Baseline activity as control (block design)	fMRI (ROI for bilateral amygdala)	Post-scan testing found patients significantly less accurate than controls, only for fearful faces, mislabelling primarily as surprised. Neurally, significant group x condition interaction: patients showed decrease in amygdala activation for fear compared to neutral, compared to controls. Explained as increase in amygdala to neutral, rather than decrease for fear.
Holt et al., 2006 [57]	Between-groups Group 1: 15 (15/0) chronic SP on	Passively viewing fearful, happy, neutral expressions.	fMRI (ROI for amygdala-hippocampal)	Significant group x condition interaction: greater activation in right amygdala and hippocampus to fearful and neutral faces in patients, relative to controls.

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	antipsychotics* Group 2: 16 (16/0) Healthy Controls	Fixation cross as baseline (block design)	complex)	
Surguladze et al., 2006 [59]	Between-groups Group 1: 15 (15/0) chronic SP on antipsychotics* Group 2: 11 (11/0) Healthy Controls	Implicit emotion perception of neutral, 50% fearful, 100% fearful facial expressions. Baseline activity as control (event- related design)	fMRI (whole-brain)	Significant group x condition interaction: for fearful and mildly fearful faces, patients showed reduced activation in right parahippocampal gyrus, compared to controls. Conversely, increased activation in right parahippocampal gyrus in patients for neutral faces, relative to controls. Significant positive association between right amygdala response to neutral faces and reality distortion in patients.
Kosaka et al., 2002 [63]	Between-groups Group 1: 12 (6/6) chronic SP, 10 were on antipsychotics* Group 2: 12 (6/6) Healthy Controls	Positive/negative face discrimination for happy, angry, disgusting, sad, neutral faces. Rectangle size discrimination task as control (block design)	fMRI (ROI approach for amygdala)	No group difference in task accuracy. Neurally, significant group x condition interaction: happy faces provoked increased activation of right amygdala in patients over controls. Negative faces activated bilateral amygdalae in patients, but only right amygdala was activated in controls, however this difference was not significant.

*Unspecified.

Abbreviations: CBT= Cognitive Behavioural Therapy; PET= Positron Emission Tomography; PPI= Psychophysiological Interaction ROI= region of interest; SAD= schizoaffective disorder; SP= schizophrenia patients; TAU= Treatment as Usual.

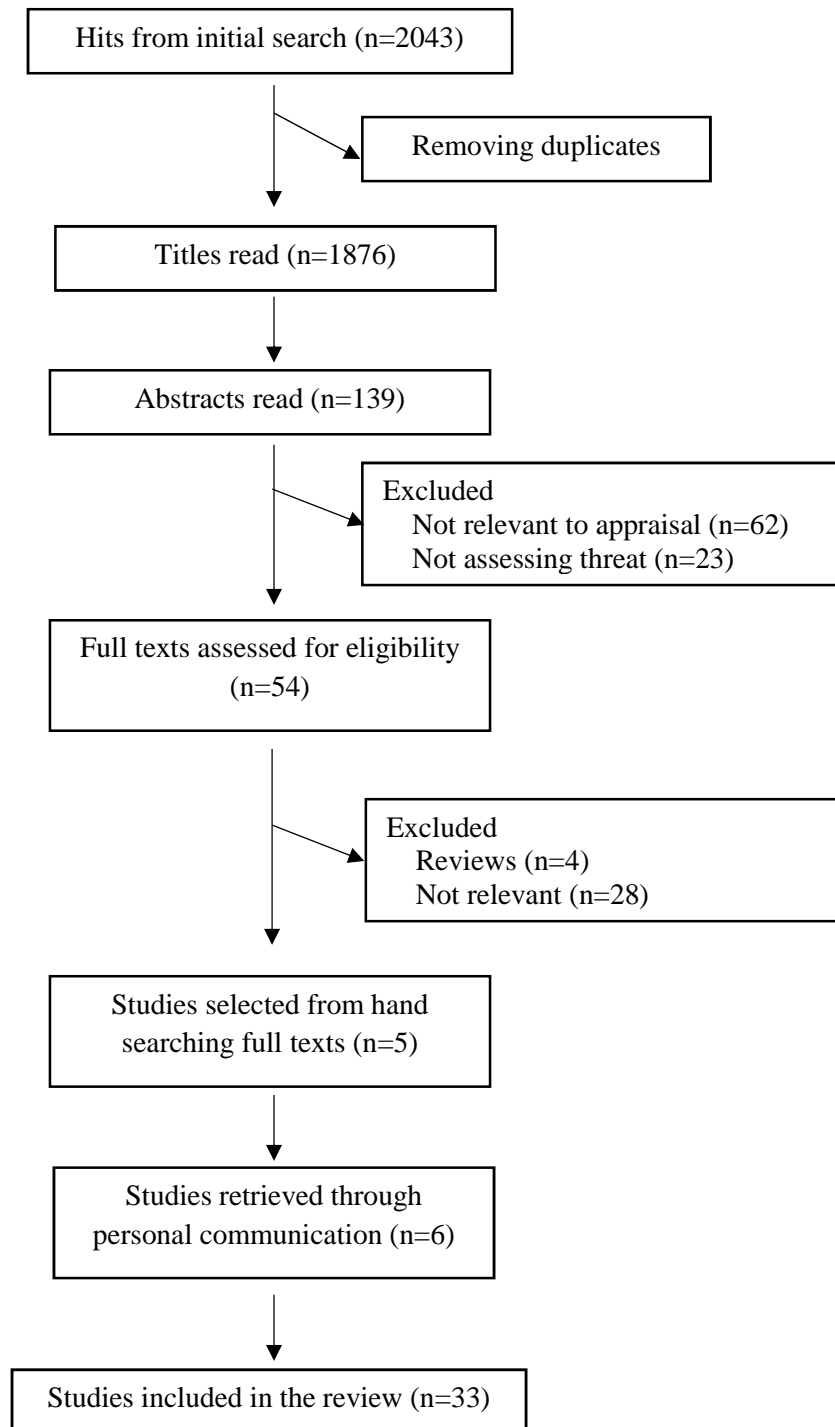


Fig. 1. Flow chart of study selection.